REMARKS

Claims 1, 2, 4-11, 14, 15, and 21-29 are pending in the application. Claim 25 has been amended. Support for the amendment to claim 25 is found throughout the specification, for example, at page 7, lines 5-7 and 14-16. Applicants respectfully assert that no new matter has been added and request reconsideration of the claims currently pending in the application.

I. Rejection under the judicially created doctrine of obvious-type double patenting

On page 2 of the Office Action, claims 1, 2, 9, 14, 21, and 29 are provisionally rejected under the judicially created doctrine of obvious-type double patenting as being unpatentable over the claims 1, 8, 10, 13, 15, 34-35, and 38-40 of copending Application No. 09/186,810.

Applicants submit that claims 1, 2, 9, 14, 21, and 29 of the present application are distinct and independently patentable from the claims of copending Application Number 09/186,810. Claims 1, 2, 9, and 29 are directed to a prosthesis for a human patient comprising allograft or xenograft tissue having a polypeptide growth factor associated therewith, and claims 14 and 21 are directed to a prosthesis heart valve comprising a substrate with associated VEGF. They are independently patentable from claims 1, 8, 10, 13, 15, 34, 35, and 38-40 of copending Application No. 09/186,810. Also, since this is a provisional rejection, Applicants will consider filing a terminal disclaimer complying with 37 CFR 3.73(b) when these claims or the allegedly conflicting claims of the copending application are found to be allowable and the rejection is no longer a provisional one. Reconsideration is respectfully requested.

II. Rejection under 35 U.S.C. §102 (b)

A. On page 3 of the Office Action, claims 25 and 28 are rejected under 35 U.S.C. §102 (b) as being anticipated by Cahalan, et al. (U.S. Patent No. 5,308,641).

The Examiner states that Cahalan, et al. anticipate the claim language when the human or animal tissue is used as the solid surface and the biomolecule is one of the growth hormones listed on col. 6, lines 14-18. The Examiner also states that "fixed" and "crosslinked" are synonymous in the tissue graft art. Further, glutaraldehyde is disclosed as one of the crosslinking agents in Cahalan, et al. (Col. 4, lines 58-62).

Applicants respectfully traverse the rejections.

Cahalan, et al. teach the use of an improved spacer material, comprising an aminated substrate, a polyalkylimine covalently attached to the aminated substrate and a crosslinking agent. See col. 3, lines 1-20. The polyalkylimine is covalently bonded to the solid surface with an activating agent which contains at least two aldehyde groups and then contacting the activated surface with the polyalkylimine. Col. 3, lines 21-26. The activating agent used can be the same as the crosslinking agent used to crosslink the polyalkylimine. Col. 3, lines 26-29. The polyalkylimine and the crosslinking agent together form the spacer that is capable of attachment to a solid surface, is large enough to extend from the surface of the solid surface, is capable of immobilizing a biomolecule or molecules, and insures that the active site of the biomolecule is held outward away from the support (substrate). See the abstract, background of the invention, and specifically col. 2, lines 12-18. Thus, the spacer material improves the biocompatibility of the substrate by intervening between the substrate and the biomolecule so that the

biomolecule is attached to the spacer and not to the solid substrate underneath. See col. 4, lines 58-60, and col. 5, lines 44-55. Sometimes, a second spacer material having at least one primary or secondary amino group extending away from the surface is used. See col. 3, lines 35-53. Cahalan, et al. also stress that in the case of coupling a cellular adhesive molecule to the solid surface or substrate, the spacer prevents the biomolecule cellular adhesive from becoming buried in the surface and losing bioactivity, further showing that the biomolecule is not attached to the substrate. See col. 3, lines 35-65, and col. 6, lines 29-51.

Controlled light crosslinking of the polyalkylimine itself prevents the biomolecule from being buried in the spacer and losing bioactivity. The light crosslinking also provides aldehyde functionality for the polyalkylimine surface that will allow biomolecules to readily bond to the spacer. Col. 4, line 68 to col. 5, line 3.

The teaching of spacers and their uses, along with the recitation of lightly crosslinking with glutaraldehyde crosslinkers, do not teach a crosslinked tissue having an exogenous polypeptide growth factor associated therewith, the subject matter of claim 25, since associating a biomolecule with a spacer is different from associating a biomolecule with a crosslinked tissue.

To anticipate a claim, the reference must teach every element of the claim. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Therefore, all

claim elements, and their limitations, must be found in the prior art reference to maintain a rejection based on 35 U.S.C. §102. Applicants respectfully submit that despite the use of glutaraldehyde in Cahalan, et al., Cahalan, et al.'s teaching of attaching a molecule to a surface by making use of an intermediary (spacer) is different from associating the biomolecule with the crosslinked tissue. Thus, since the spacer is intermediate between the solid substrate and biomolecule, Cahalan, et al. do not teach every element of claim 25, and therefore fails to anticipate claim 25.

Dependent claim 28, which is dependent from independent claim 25, was also rejected under 35 U.S.C. §102(b) as being unpatentable over Cahalan, et al. While Applicants do not acquiesce with the particular rejections to the dependent claim, it is believed that these rejections are moot in view of the remarks made in connection with independent claim 25. Claim 28 includes all of the limitations of the base claim and any intervening claims, and recites additional features which further distinguish it from the cited references. Therefore, dependent claim 28 is also in condition for allowance.

Applicants respectfully request withdrawal of the rejection of claims 25 and 28 under 35 U.S.C. §102 (b) as being anticipated by Cahalan, et al.

B. On page 4 of the Office Action, claims 25 and 26 are rejected under 35 U.S.C. §102 (b) as being anticipated by Bayne, et al. (EP 0 476 983). The Examiner asserts that Bayne, et al anticipate the claim language wherein the fibrin coating is applied prior to or in addition to the VEGF II growth factors to the surface of the fixed umbilical vein. See abstract, page 8, lines 14-26 and page 8, lines 20-23. The Examiner posits that the

tubular supports coated with VEGF II include fixed umbilical cord vein and thus, the claim language is fully met.

Applicants respectfully request reconsideration.

Bayne, et al disclose two embodiments of promoting cell growth. The first one involves the growing of cells in vitro on culture medium and then plating the cells onto the inside surface of the fixed umbilical vein after an adequate number of endothelial cells are grown in vitro on culture medium in the presence of VEGF II and any other supplement required for cell growth. See page 8, lines 14-19. The second or alternative one involves implanting the artificial tubular support coated with VEGF, and "(f)ollowing implantation, endothelial cells ...grow on the **artificial surface**. Prior coating of the **artificial vessel** ...with proteins such as fibrin ...enhance attachment of the cells to the **artificial surface**." (emphasis added) (page 8, lines 17-23). In this alternate embodiment, there is no mention of fixed umbilical vein as the support. To posit that the fixed umbilical vein could be included as the tubular support so that the claim language could be met would be employing circular reasoning. The fact is that Bayne, et al do not disclose application of a growth factor to a fixed umbilical vein as the tubular support coated with VEGF II. Only the coating of artificial surfaces with fibrin or VEGF II is disclosed or taught. Since the Bayne EP application does not disclose every element of the claimed invention, the Bayne EP application does not anticipate claim 25.

Claim 26 depends from claim 25 and therefore incorporates all the limitations of claim 25 and is also not anticipated by Bayne, et al.

Applicants respectfully request withdrawal of the rejection of claims 25 and 26 are rejected under 35 U.S.C. §102 (b) as being anticipated by Bayne, et al.

III. Rejection under 35 U.S.C. § 103(a)

A. Claims 25 and 26 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bayne, et al. alone. The Examiner asserts that if the tubular supports coated with VEGF II do not include umbilical cord vein, then it would have been obvious to use umbilical vein as the tubular support.

Applicants respectfully traverse the rejection.

As already discussed above, Bayne, et al. disclose the plating of cells to the fixed umbilical vein after the cells are grown on culture medium in the presence of VEGF II and other elements needed for such growth. It does not teach the association of crosslinked tissue with a polypeptide growth factor, in particular with VEGF, to stimulate cell growth on the tissue, but only the association of VEGF II with an **artificial surface.** See page 8, lines 20-23. When referring to a fixed umbilical vein, no mention is made of prior coating of the umbilical vein with VEGF II or a protein like fibrin. While Bayne, et al disclose the use of fibrin to improve the attachment of cells onto **artificial surfaces**, the **artificial surfaces** are not fixed umbilical cord veins, since Bayne, et al. made clear that after sufficient number of cells are grown on the culture medium, the cells are then plated onto umbilical cord veins. Page 8, lines 18-19. Therefore, Bayne, et al. does not teach, suggest or motivate application of VEGF with a crosslinked **natural** tissue, Bayne only teaches VEGF with an **artificial surface**.

Three criteria must be met to establish a *prima facie* case of obviousness. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the

reference. Second, there must be a reasonable expectation of success. Finally, the prior art reference, or combination of references, must teach or suggest all the claim limitations. MPEP § 2142. Applicants respectfully submit that the prior art fails to disclose all the claim limitations and there would be no motivation to combine the references as proposed by the Examiner. The Examiner cannot use hindsight construction and circular argument to posit that even if the tubular supports coated with VEGF II do not include fixed umbilical vein, it would have been obvious to use the fixed umbilical vein as the support based on Applicants' invention. If Bayne, et al. believed that cells could have been grown on the fixed umbilical vein tissue through the association with growth factors, Bayne, et al. would not have taught the complicated mechanism of growing cells on an artificial surface and then plating them onto the fixed umbilical cord vein. Thus, Bayne, et al. do not render claim 25 obvious.

Dependent claim 26, which is dependent from independent claim 25, was also rejected under 35 U.S.C. §103(a) as being unpatentable over Bayne, et al. While Applicants do not acquiesce with the particular rejections to the dependent claim, it is believed that these rejections are moot in view of the remarks made in connection with independent claim 25. Claim 26 includes all of the limitations of the base claim and any intervening claims, and recites additional features which further distinguish the claim from the cited references. Therefore, dependent claim 26 is also in condition for allowance.

Applicants respectfully request that the rejection of claims 25 and 26 under 35 U.S.C. §103(a) be withdrawn.

B. On page 4 of the Office Action, claims 1, 2, 4, 5, 9-11, and 29 are rejected as being unpatentable over Bayne, et al. in view of Wadstrom (U.S. Patent No. 5,631,011). The Examiner asserts that Bayne, et al. discloses an implant having a fibrin coating (biologic adhesive) that is applied prior to the application of VEGF II growth factor (which is the polypeptide growth factor as claimed), and that the fixed umbilical cord vein, although a crosslinked human or animal tissue, is not clearly either an allograft or xenograph as claimed, i.e., the tissue of Bayne, et al. is generic to both allograft or xenograft tissues. Nonetheless, it is the Examiner's position that it would have been considered clearly obvious to an ordinary artisan to use an allograft or xenograft tissue for the cord vein of Bayne, et al absent some showing of criticality therefor. In addition, the Examiner cited Wadström to show that fibrin is a common biologic tissue adhesive. See the abstract and col. 1, lines 1-20. Thus, the fibrin coating of Bayne, et al can be called and would function as a biologic adhesive as claimed.

Applicants respectfully traverse the rejections.

Bayne, et al. does not disclose a polypeptide growth factor or protein such as fibrin associated with the umbilical vein, as already discussed above. Instead, Bayne, et al. teach the association of VEGF II or fibrin with an **artificial surface.** See page 8, lines 20-23. When referring to a fixed umbilical vein, no mention is made of prior coating of the umbilical vein with VEGF II or a protein like fibrin. While Bayne, et al. disclose the use of fibrin to improve the attachment of cells onto artificial surfaces, the artificial surfaces are not fixed umbilical cord veins, since Bayne, et al. made clear that after sufficient number of cells are grown on the culture medium, the cells are then plated onto umbilical veins. This teaching does not motivate one of ordinary skill in the art to look for

a biologic adhesive, whether it is called a fibrin adhesive or not, to attach growth factors to allografts or xenografts. This deficiency in Bayne, et al. is not supplied by Wadström, as Wadström also does not teach, suggest, or motivate association of a polypeptide growth factor with tissue. Wadström only teaches how to improve fibrin glue so that it does not have a low viscosity problem and also teaches how such an improved glue promotes wound healing without scar formation or development of adhesions. See col. 2, line 66 to col. 3, line 48. Even if Wadström is considered not directed to an anti-adherence composition, and that fibrin is an adhesive (Bayne, et al. teach that fibrin is a protein on page 8, line 23), and that there is motivation to combine the teaching of Bayne, et al. with that of Wadström, the combined teaching does not teach or motivate one of ordinary skill in the art to arrive at the invention of claims 1 and 29. Since Bayne, et al. is directed to coating of VEGF on artificial surfaces and not tissues, the Examiner cannot use the hindsight knowledge of Applicants' invention to supply the motivation to jump from artificial surfaces to fixed umbilical veins. In addition, if Bayne, et al. believed that it would have been possible to coat VEGF onto fixed umbilical veins to stimulate cell growth, they would not be proposing the complicated process of growing cells onto artificial surfaces and then removing them and plating them onto umbilical veins. The combined teachings, without Applicants' invention, do not teach, suggest or motivate the association of polypeptide growth factor with tissue. Therefore, claims 1 and 29 are not obvious based on Bayne, et al. in view of Wadström.

Claims 2, 4-5, and 9-11 are dependent from claim 1. While Applicants do not acquiesce with the particular rejections to these dependent claims, it is believed that these rejections are moot in view of the remarks made in connection with independent

claim 1. These dependent claims include all of the limitations of the base claim and any intervening claims, and recite additional features which further distinguish these claims from the cited references. Therefore, dependent claims 2, 4-5 and 9-11 are also in condition for allowance.

Applicants respectfully request the withdrawal of the rejection of claims 1-2, 4-5, 9-11, and 29 as being unpatentable over Bayne, et al., in view of Wadström.

C. On page 5 of the Office Action, claims 6-8, 14, 15, 21-24, and 27-28 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bayne, et al. and Wadstrom as applied to claims 1-5, 9-11, and 29 above, and further in view of Carpentier, et al. (U.S. Patent No. 4,648,881). The Examiner admits that Bayne, et al. do not disclose uncrosslinked tissue, the heart valve form of the tissue, or the other tissue types as claimed. However, the Examiner states that Carpentier, et al. teach that all uncrosslinked and crosslinked forms of tissue, heart valve tissue forms and other types of tissue are well known in the art. See col. 2, lines 3-15. Hence the Examiner's position is that it would have been obvious to use these materials as the substrates of Bayne, et al. implants into other shapes in order to make it useful in other sites and broaden its applicability.

Applicants respectfully traverse the rejection.

The discussion above for claims 1-2, 4-5, 9-11, and 29 with regard to Bayne, et al. and Wadström also applies here. Bayne, et al. not only do not disclosed uncrosslinked tissue, the heart valve form of the tissue, or the other tissue types as claimed, Bayne, et al. also do not disclose the association of growth factors with tissues at all, as noted

above, crosslinked or uncrosslinked. Therefore, the deficiency in Bayne, et al. is not just that uncrosslinked tissue, the heart valve form of the tissue, or the other tissue types as claimed are not disclosed or taught, but that no association of growth factors with tissue of any kind is disclosed or taught. Wadström does not supply the deficiency, and the disclosure in Carpentier, et al. of tissue calcification does not motivate one of ordinary skill in the art to arrive at the invention of claims 1, 14 and 25. Since the deficiency of Bayne, et al. is not supplied by Wadström in view of Carpentier, et al. without using Applicants' invention as a road map, there is just no teaching or motivation in the cited references to guide one of ordinary skill in the art to arrive at the invention of claims 1, 14, and 25.

Claims 6-8, 15, 21-24, and 27-28 are dependent from independent claims 1, 14, and 25 and were also rejected under 35 U.S.C. §103(a) as being unpatentable over Bayne, et al. and Wadstrom as applied to claims 1-5, 9-11, and 29 above, and further in view of Carpentier, et al. (U.S. Patent No. 4,648,881). While Applicants do not acquiesce with the particular rejections to these dependent claims, it is believed that these rejections are moot in view of the remarks made in connection with independent claims 1, 14, and 25. These dependent claims include all of the limitations of the base claim and any intervening claims, and recite additional features which further distinguish these claims from the cited references. Therefore, dependent claims 6-8, 15, 21-24, and 27-28 are also in condition for allowance.

Applicants respectfully request withdrawal of the rejection of claims 6-8, 14, 15, 21-24, and 27-28 under 35 U.S.C. § 103(a) as being anticipated by Bayne, et al. and

Wadstrom as applied to claims 1-5, 9-11, and 29 above, and further in view of Carpentier, et al.

IV. Response to arguments

1. Issue A

Applicants have already addressed this issue above.

2. Issue B

Applicants have already addressed this issue above. In addition, in response to the Examiner's assertion that all the claim limitations are met so that Cahalan's overall purpose for the invention is not relevant, and that once Cahalan attaches polyalkylimine to the tissue, it becomes part of the tissue, Applicants submit that since Cahalan, et al. is concerned with using a spacer that is present between the substrate and the biomolecule, Cahalan, et al's disclosure is not related to association of growth factors with tissue, but is related to attaching biomolecules to spacers. A spacer is not a crosslinked natural tissue. Therefore, Cahalan, et al. do not disclose every element of the present invention of claims 25 and 28, as fully discussed above.

3. Issue C

Applicants have fully addressed this issue above and further submits that Bayne, et al. do not motivate the subject matter of claims 25 and 28 since there is no motivation or expectation of success that a treatment for synthetic blood vessels can translate into a treatment for crosslinked natural tissue. Further, if Bayne, et al. had believed that growth

factors could be directly associated with tissue to promote cell growth, they would not have gone to the trouble of growing cells on synthetic supports and then plating the cells onto fixed umbilical veins.

4. Issue D

This issue has also been fully discussed above. Whether fibrin is or is not an adhesive, the deficiency of Bayne, et al. as discussed above concerning Issue C is not supplied by Wadstrom, as Bayne, et al. believe that the cells must be grown elsewhere prior to plating them onto fixed umbilical veins, and the disclosure of a fibrin adhesive or anti-adherent cannot change the fact that plating ready made cells onto umbilical veins is not the same as or does not motivate the promotion of cell growth by associating growth factors with tissue.

V. Conclusion

In view of the amendments and reasons provided above, it is believed that all pending claims are in condition for allowance. Applicants respectfully request favorable reconsideration and early allowance of all pending claims.

If a telephone conference would be helpful in resolving any issues concerning this communication, please contact Applicants' attorney of record, Hallie A. Finucane at (952) 253-4134.

Respectfully submitted,

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